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# Facilitating individuals and families affected by fragile X syndrome to participate in medication trials

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## Abstract

**Background** Recently, there has been an increasing number of trials of medications for fragile X syndrome (FXS). In order to be adequately powered, trials have involved many centres around the world with relatively small numbers of participants recruited at each site. This study aims to understand the barriers to, and how best to facilitate participation in, medication trials in order to improve recruitment and the experience of participants with FXS.

**Methods** A mixed methods design was used to collect both quantitative and qualitative data. Participants were invited to participate through the UK Fragile X Society, a local mailing list and through social media. Those who agreed to participate completed a quantitative questionnaire and indicated whether they would be willing to participate in a follow-up focus group.

**Results** The questionnaire was completed by 328 individuals who either had FXS, or were a parent, carer or family member of an individual with FXS. Over two-thirds of participants reported concern about side effects, while over one-third mentioned swallowing tablets, blood tests, financial aspects and travel as barriers to participation. Focus groups with 12 individuals highlighted themes of trial challenges,

strategies to overcome these and motivating factors to participate.

**Conclusions** Many of the factors, which potentially negatively influence participation in a clinical trial for FXS, could be mitigated in relatively simple ways.

Easily accessible information, particularly about safety issues, the research team and the trial environment should be standard practice.

Desensitisation programmes for blood testing, provision of different preparations of medication (e.g. liquid) and use of a combination of local, remote and site visits to reduce travel and time should also be considered.

**Keywords** clinical trials, fragile X syndrome, participation, recruitment

## Background

Fragile X syndrome (FXS) is the most common known inherited form of intellectual disability (ID) with a prevalence of 1.4 per 10 000 male and 0.9 per 10 000 female patients (Hunter *et al.*, 2014). The physical presentation of the condition is well described, although the exact features may vary considerably between patients. (Hagerman and Hagerman, 2002; Kidd *et al.*, 2014). ID in people with FXS can vary from mild to severe; however, it is most commonly within the moderate range, with male patients often more affected than female patients. In addition to the characteristic physical features and ID, individuals with FXS also commonly present with a

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number of behavioural features, which include hyperactivity, anxiety and autistic traits (Tsiouris and Brown, 2004).

As with other forms of ID, the management of FXS is multidisciplinary in nature. Medication can have a role to play for some individuals, but at present, the medical treatments used are primarily symptomatic in nature. These include the use of selective serotonin reuptake inhibitors for anxiety, stimulants for attention deficit hyperactivity disorder and antipsychotics for irritability or aggressive behaviour (Tsiouris and Brown, 2004). In recent years, there has, however, been an increase in the number of medications suggested to target the underlying neurobiology of FXS, and subsequently, a number of these have been brought to clinical trial (Krueger and Bear, 2011; Lee *et al.*, 2018).

Participation in clinical research by people with ID is known to be associated with particular difficulties, such as identifying and recruiting appropriate participants, obtaining informed consent and difficulties associated with study procedures (Oliver-Africano *et al.*, 2010). These difficulties are likely to be amplified for clinical treatment trial participation, as individuals are often required to attend trial sites on multiple occasions and undergo invasive procedures, such as blood sampling. It is notable that the largest clinical trials that have occurred in FXS have required multinational efforts to recruit a relatively small number of participants (Berry-Kravis *et al.*, 2016; Hagerman *et al.*, 2018; Youssef *et al.*, 2018). Not only are such trials complex to manage and expensive to run, they also introduce risks to trial fidelity, in particular intersite variability in clinical assessments.

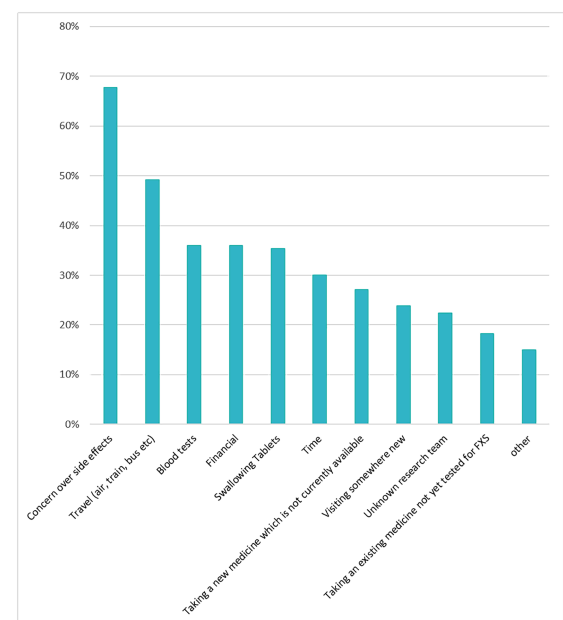
There is therefore a need to understand the factors that affect participation in clinical trials of medications for FXS, to increase the feasibility of conducting future trials. A number of previous studies have used either survey-based or qualitative interview-based methods to examine parental attitudes towards pharmacological trials in FXS (Chechi *et al.*, 2014; Reines *et al.*, 2017; Richstein *et al.*, 2017; D'Amanda *et al.*, 2019). These have suggested that concerns about medicating children, issues around consent, logistical burdens and invasive trial procedures are seen as barriers to participation, whereas altruistic motives and therapeutic optimism are potential motivating factors. While informative, a potential limitation of these studies is that they have

occurred in relatively small groups of people and/or have been recruited through single specialist centres and so may not be representative of the broader population of people with fragile X and their families. We therefore set out to investigate the barriers to participation in drug trials and how these could be overcome in a large population of families affected by FXS recruited from diverse sources.

## Methods

### Data collection

A mixed methods design was used, collecting both quantitative and qualitative data. A quantitative questionnaire was completed by parents, carers, family members of individuals with FXS or by people with FXS themselves. Carers were permitted to assist those with FXS to complete the questionnaire. The questionnaire contained seven questions (Supporting Information). These examined any previous involvement with clinical trials, willingness to consider taking part in future clinical trials, potential barriers to trial participation (with 11 possible



**FIGURE 1.** Proportion of all respondents endorsing each item as a potential barrier to clinical trial participation. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

responses – Fig. 1), concerns regarding medical trials and what could be done to encourage participation.

At the end of the survey, participants indicated if they were willing to take part in a follow-up focus group. Those who consented were then invited to one of three focus groups, located around the United Kingdom. For the focus groups, a number of prompts were developed around which the discussion was framed. Specifically, they were asked about their current understanding of clinical trials and what they would want to know before deciding whether or not to take part in a trial. They were also asked to imagine they were designing a clinical trial and what they would take into consideration.

### Recruitment

Recruitment proceeded through three sources. Firstly, paper copies of the questionnaire were sent to over 1000 families through the UK Fragile X Society, the main support organisation for families with FXS in the United Kingdom. In addition, an email with a link to an online questionnaire was sent to individuals registered with The Patrick Wild Centre research centre at the University of Edinburgh. Finally, a link to the online version of the questionnaire was advertised on the research centre website, Facebook page and Twitter feed.

In order to participate, all individuals had to be over the age of 18 and either be a family member or a carer of someone with a diagnosis of FXS or have FXS themselves.

Ethical approval for the study was granted by the Accord Medical Research Ethics Committee at the University of Edinburgh. Consent for the questionnaire was implied through its completion; written informed consent was collected from individuals who took part in the focus groups.

### Quantitative analysis

The analysis for the questionnaire data was conducted using IBM Statistical Package for Social Science (SPSS) (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The primary results were considered using descriptive statistics. Chi-squared tests were used to determine whether or not an expressed interest in taking part in clinical trials made a difference to the barriers reported.

### Qualitative analysis

The focus group data were analysed using a thematic analysis approach (Braun and Clarke, 2006). Following completion of all focus groups, the audio recordings were transcribed. Initial codes were generated from the data, and these were sorted into draft thematic groups. These draft thematic groups were then reviewed and refined after considering the validity of each theme in relation to the whole data set until final themes were generated and a thematic map was developed. This process was conducted by both the researcher who facilitated the groups (SE) and a researcher external to the study team (SH). NVIVO software (QSR International Pty Ltd. Version 10, 2012) was used to collate, organise and analyse the generated codes.

## Results

### Questionnaire results

A total of 328 people completed the questionnaire; 94.5% were parents of individuals with FXS, 3.3% were carers and 2.2% had a diagnosis of FXS. Nineteen per cent of people had previously taken part in a drug treatment trial of new medicines. Of the people who had taken part in a previous trial, 61% had a positive experience, 33% reported having a mixed experience and 3% had a negative experience.

Out of all the participants, 45.7% stated they would consider participating in future clinical trials, 42.5% would maybe consider participating and 11.8% would not consider it. Those who had previously participated in trials were significantly more likely ( $P = 0.02$ ) to take part in a future trial, with 62% of those who have previously taken part expressing they would consider participating in a future trial, compared with 40% of those who had not previously taken part.

Figure 1 summarises the barriers to participation highlighted through the questionnaire. The most commonly reported barrier was concern over side effects, which was endorsed by over two-thirds of participants, while over one-third of participants reported potential difficulties with trial procedures (swallowing tablets and blood tests) or practicalities (financial aspects and travel) as barriers to participation. Of those who endorsed the 'other' category, novel responses that were not covered

elsewhere in the questionnaire included concern about seeing benefits from a trial then having to stop the medication, difficulties participating due to their child not living with them and not being made aware of trials.

Table 1 shows the barriers identified by participants and compares the barriers identified in those who would be willing to participate in a future trial and those who would not. For six of the barriers, there was a significant difference ( $P < 0.05$ ) between those who reported that they would or would not consider taking part in a clinical trial.

Those who said they would not participate in future trials more frequently reported the following as barriers to participation: taking a new medicine, taking an existing medicine that was not yet licensed in FXS, having to undergo blood tests and visiting a new place and the risk of side effects. Those who said they would or maybe would participate in future trials more frequently reported travel as a barrier.

### Qualitative findings

A total of 182 people who completed the questionnaire indicated willingness to be part of a focus group. The focus groups took part in three

**Table 1** Proportion of individuals, divided by willingness to participate in future trials, reporting which items would be a barrier to participation (significant differences highlighted in bold).

Variable	Willing to participate in future trials			$\chi^2$	$P$
	Yes (%)	No (%)	Maybe (%)		
New medicine	13.3	48.6	33.1	25.42	<b>&lt;0.001</b>
Existing unlicensed medicine	7.0	40.5	22.6	26.81	<b>&lt;0.001</b>
Blood tests	26.6	40.5	39.8	6.26	<b>0.04</b>
Travel	43.4	32.4	54.9	7.24	<b>0.03</b>
Unknown research team	17.5	27.0	24.8	2.87	0.24
New place	16.1	27.0	29.3	7.20	<b>0.03</b>
Swallowing medication	30.1	29.7	39.1	2.83	0.24
Time	23.8	35.1	33.1	3.64	0.16
Financial	31.5	21.6	39.8	4.97	0.08
Side effects	55.9	81.1	69.2	10.29	<b>0.006</b>

For example, 13.3% of those people who were willing to participate in a future trial endorsed concern about taking a new medication as a significant barrier to participation, whereas this concern was endorsed by 48.6% of those who indicated they were unwilling to participate in a future trial.

locations throughout the United Kingdom to ensure as many people could take part as possible. A total of 52 invitations were sent, with 12 individuals agreeing to participate. Of the people who took part, 11 were parents, 1 was a carer of an individual with FXS and none of the participants had FXS themselves.

Data from the transcribed interviews were initially split into 115 codes, which were then split into six categories and then grouped into themes, each with several subthemes. The three major themes that emerged from the data were trial challenges/barriers, strategies to assist participation and motivating factors. The main themes and subthemes identified following the coding are shown in a thematic map in Fig. 2. Each of the three themes are discussed in turn below.

#### Theme 1: Trial challenges/barriers

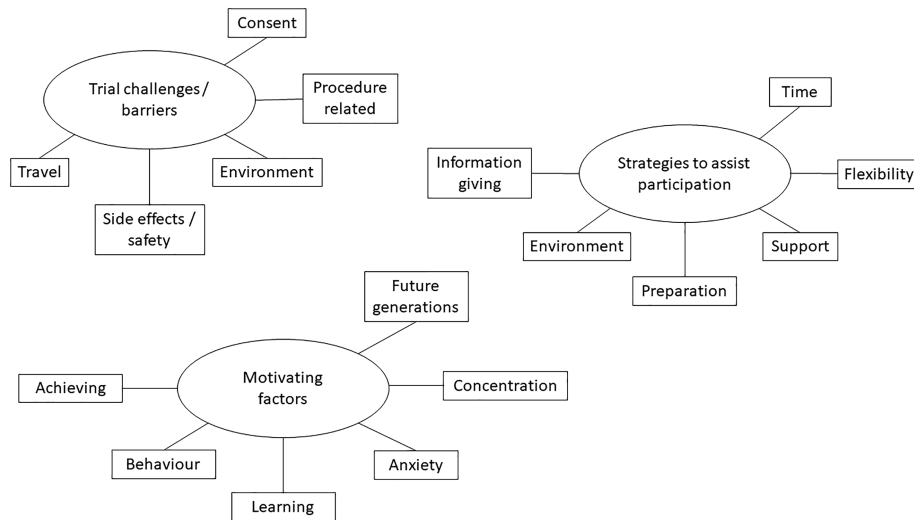
**Travel.** Travel was primarily seen as being an issue due to the time it would take and the interruption to the trial participant's routine. This was particularly reported to be the case if several research appointments were required:

It would have to be local I don't have time to travel ... My boy loves travelling but we just can't afford the time It was mentioned in several of the focus groups that being given the option to travel together in a group would help to relieve some of the anxieties regarding potential travel issues:

Travelling with Fragile X is not, oh it's a joy (laughter) It would be friendly ... it would be an anxious situation but if you knew you were going to fly together and meet at the airport ... It was also mentioned that if the travel could be arranged for them so they did not have to organise it themselves, this would be helpful:

it's all taken care of so you don't have to worry about it"

**Procedure-related difficulties.** There were many concerns raised around the participant's ability to have their blood taken, being able to take medication and to cope with other trial procedures. Many parents



**FIGURE 2.** Themes and subthemes identified through the thematic analysis.

talked about previous experiences trying to give their child medications in different forms and discussed the need for researchers to have options available:

My daughter will not and cannot take any medication in the form of tablets Taking blood came up as a barrier in all three focus groups and was repeatedly brought up on different occasions throughout each group:

I nearly had my fingers broken while [child] has been having their blood taken However, parents recognised the importance of bloods for safety reasons and would not want this compromised. They expressed the wish for education about why the blood test was required and whether each one was a core part of the trial or an optional add-on (as has been the case in some trials):

They are important so I am not sure they could be reduced in a trial I think they need to tell you why they do the blood tests then you would know

*Side effects/safety.* The focus groups confirmed that potential side effects and toxicity of a new medication is of primary concern:

Safety is number one I am very, very wary of the toxicity One participant commented on the issues they had had in previous trials that have had a knock-on impact on future participation. The participant focused on their child's inability to verbally express the issues and side-effects she was experiencing:

[child] Non-verbal ... so when you're talking about drug trials... [child] would cry and you wouldn't know why The overall concerns of taking new medications, which may have unpredictable side effects, were effectively summarised by one participant who stated that

I think a lot of people want to help but then they just don't know how their child is going to react

*Environment.* The environment relates to where the trial should take place. There were some participants that would favour the trial being done in their own home as it would mean they did not have to travel and would take up less time. They also felt their child may be more relaxed.

I think it would have to be local familiar territory Based at home would be nice However,



other participants felt it would be better to go somewhere else outside their home in case there were any negative consequences associated with the trial that they did not want to be associated with home:

I don't want home being associated with blood tests

*Consent.* As the majority of people attending the focus groups were parents to a child with FXS, one of the main concerns was over them consenting on behalf of their child.

Saying yes for someone else is a big responsibility. Do whatever you want to me but my child is different. While the parents understood that legally they were able to consent on behalf of their child, they were concerned that their child would not be able to understand why they would be taking part.

I don't think he would really understand why we were doing it so that's not informed consent is it? I don't think he would understand what I was trying to explain to him

## *Theme 2: Strategies to assist participation*

The main subthemes that came out were information giving, environment, preparation, support, flexibility and time.

*Information giving.* The focus groups made it very clear that they wanted as much information on the trial medication as possible, and having this information would help alleviate anxieties about side effects and safety. They also reported wanting easily understandable information broken into small sections. It was suggested to have a short and long information sheet, so if someone was interested, they could access more detailed information. The participants felt if they had sufficient information about the trial medication and were made aware of previous safety trials and potential side effects, then they could weigh these up and would be more likely to participate:

... sign up for it straight away if something had already gone through safety trials. I'd have more worries about a completely new drug than one that's already been used and obviously the side effects were known

Many people reported wanting to meet the research team and have the opportunity to ask questions in an informal environment with the chance to listen to other people's questions. They also felt this was important to build a trusting relationship with researchers.

It was also reported that families did not necessarily feel they could contact the researcher to discuss the trial in more detail, despite adverts and information sheets explicitly inviting this. They reported that if they were to see something negative in the information sheet, this could lead them to dismiss the trial without further consideration, rather than contacting the research team. Information events would help to reduce this risk by giving families the chance to discuss concerns in more detail in a neutral environment:

I think families want to meet you and talk

*Environment.* While environment was discussed under barriers to participation, it was also felt that this could assist participation in clinical trials through enabling people with FXS to become comfortable in clinical environments, which would be especially useful if they were local:

Local hospitals, local clinicians ... local clinicians getting to know them, actually that would be good for us

*Preparation.* Before taking part in a clinical trial, many of the participants mentioned the importance of preparing their child to help them understand what they were going to be doing and why. It was discussed that if the trial team could provide easy to understand information, they could share with their child that would be very beneficial:

A story board of what is going to happen. It was also highlighted that if their child was well prepared for blood tests, then this would be beneficial and make future routine tests at the doctors much easier:

Education packs for kids so that they understand the process of taking blood. Win: you get the blood sample, we get a kid that is probably going to be able to give blood in the future

*Support.* In each group, there was a positive discussion towards participating in research studies at the same time as other families to gain social support and have contact with families in a similar situation to themselves.

you could make friends locally. It was mentioned that travelling with others would not only take away the stress but would also be a good opportunity to get social support from other families:

With other families, they understand so I can just relax a bit

*Flexibility.* Flexibility of the trial was mentioned frequently. Participants discussed in particular the barrier of their child's ability to take medication and that flexibility around preparation (e.g. if the trial drug could be given via a patch, liquid or suppository) would make a big difference to whether or not their child could take part:

If it's drugs, personalise the method of administration. It was also suggested that being flexible with trial visit location would be helpful, especially if the primary site was some distance from their home:

You need a combination don't you? You need something you do locally ... then maybe a biannual trip further afield. Also, being flexible with regards to the testing required could make a difference, for example taking blood in a different way such as using a finger prick sample or if possible take samples less often:

Find a different way to get bloods that would be good

*Time.* Related to the above, it is important to take into account the distance to be travelled when

designing the visit schedule. Families reported being prepared to travel to a research appointment every few weeks if the appointment was nearby but most would not manage this frequency if it was further away and required more time:

Within an hour's travel might work

### *Theme 3: Motivating factors*

There were many different motivating factors for parents/carers wanting their dependant to take part in clinical trials; however, the same reasons were echoed in every focus group: therapeutic optimism and altruism. Importantly, many did not want their child to fundamentally change but rather to see improvements in certain areas of their lives such as anxiety, learning and concentration:

the biggest thing for my son is anxiety. Anxiety and concentration. They wanted their child to be able to achieve more, not necessarily in terms of their cognitive abilities, but rather to be able to go into social situations or crowded places without feeling uncomfortable, thus allowing them to live a fuller life:

Anything that helps my daughter to be able to say her own name ... anything that helps her achieve a bit more in life. Finally, the importance that clinical trials take place to further understand FXS and to help the next generation was echoed in each focus group:

Trials have to be looked at as positive. If we didn't try things we wouldn't get anywhere would we?

## **Discussion**

In this study, we set out to expand upon the current literature by using a mixed methods approach to examine barriers to clinical trial participation in FXS and how they might be overcome. We found that concern over potential side effects was the most commonly reported factor to potentially negatively affect participation in clinical trials. Concerns over the study procedures and the effects of the study on wider life were also important potential barriers to



participation. Further exploration during the focus groups highlighted that these barriers had significant complexities to them and revealed potential strategies by which they may be overcome.

While the current study collected data only on individuals with FXS, it is possible, indeed likely, that at least some of our findings could be extended to other groups of people with ID. Given the notably high rates of autism in FXS it may be that certain aspects, such as difficulty coping with a new environment or research team, would be more common than in other forms of ID. However, we would anticipate that other concerns around safety and trial procedures would be generalisable beyond FXS. Future research should compare findings between different syndromes, non-syndromic ID and idiopathic ID to identify both syndrome specific factors and those which are applicable more broadly.

### Study procedures

Concern about potential side effects was the most frequently reported barrier, which is consistent with previous literature, both in FXS (Chechi *et al.*, 2014; Reines *et al.*, 2017; D'Amanda *et al.*, 2019) and more generally (Ross *et al.*, 1999; Oliver-Africano *et al.*, 2010; Chechi *et al.*, 2014), where side effects have been reported to be one of the largest barriers to participation in clinical trials. The focus groups reported that this concern was particularly pertinent in FXS due to the presence of communication difficulties, that is families were concerned that their child may have difficulty reporting side effects and that these may then be expressed as distress or difficult behaviour.

Interestingly, the focus groups revealed that families do not expect drug trials to be risk free; however, they were very keen to receive as much information as possible so that they can make a fully informed decision. Providing such information in an open and transparent manner may therefore go some way towards diminishing their concerns.

From the quantitative questionnaire, the need for blood tests was frequently highlighted as a barrier to trial participation. However, when blood tests were discussed in the focus groups, families recognised the importance of safety bloods and understood their necessity. It was proposed that a good way to

overcome concern about phlebotomy would be to provide education packs in advance to prepare the participant with FXS. In addition, the possibility of using the trial as an opportunity to do desensitisation work around blood-taking was raised as a potentially positive aspect of participating, and that for some, it may be a motivator.

Taking part in a clinical trial with an unknown research team in an unfamiliar environment was highlighted by around a fifth of those who completed the questionnaire. This rate was consistent regardless of whether they stated they would or would not like to take part in a future trial (Table 1), suggesting that this factor may not have a strong impact as to whether someone chooses to take part or not. In focus groups, families discussed that it would be preferable for the affected individual to meet the research team beforehand to help ease anxiety. Ideally, research could be conducted by local clinicians so the individual with FXS could build up a relationship with these clinical teams.

Swallowing medication was reported as a barrier by 35% of participants. The same percentage of people reported this as a barrier regardless of whether or not they would choose to take part in a future clinical trial. In focus groups, different methods of medication administration were discussed, and it was clear that flexibility in administration methods would maximise participation.

Interestingly, potential randomisation to a placebo arm was not described as a barrier to participation in this study. This was somewhat surprising given that previous research has suggested that this may be a factor in trial participation for other conditions (Welton *et al.*, 1999; Bardakjian *et al.*, 2019) and that recruitment may be easier when participants are informed what they are taking (Treweek *et al.*, 2018). Our lack of findings in this area may relate to methodological issues, specifically that we did not include this as a suggested barrier in our questionnaire. It should be noted however that the issue of placebos was raised during the focus groups but was not considered by participants to have any effect on their willingness to participate, suggesting that the potential for being randomised to the placebo arm is not a significant barrier to participation in this group.

### Effects of study on wider life

The second most commonly reported barrier to participation was travel (49%). From the focus group discussions, it was clear that these concerns were not simply about the mode of transport and associated anxiety but also included the time involved, the frequency of appointments and possible interruption to routine. People reported that it was reasonable to travel short distances on a regular basis and would be willing to travel further for more infrequent visits. It was also suggested in a questionnaire response that visits conducted remotely would make participation easier and encourage others to take part in new trials. Many were open to the idea of travelling with their child, particularly if they could do this with other families who could provide peer support. It is interesting to note that despite travel being reported as one of the main barriers to participation, 44% of people who cited this as a potential barrier would still consider taking part in a clinical trial.

Financial impacts were also reported as potentially important barriers to participation. The results from the focus groups showed that some families were unaware that all travel and subsistence would be covered, indicating the importance of providing early reassurance about this. It should be noted that financial concerns also extended to indirect factors, not commonly covered in trial budgets, such as taking time off work.

### Overcoming barriers

In addition to the ways of overcoming specific barriers discussed above, one factor that came up repeatedly in each focus group was the importance of having accessible information to help families to understand the study. Particularly, having information on any potential safety issues and having it presented in a variety of easy-to-understand formats were felt to be important ways to facilitate participation. The respondents felt that a good way to get information on the study would be to meet the research team at information evenings and to have an opportunity to ask questions in an informal setting. This was felt to be less daunting than directly contacting a researcher in response to an invitation to take part. The families suggested that if questions could be asked at an early stage then this would help to reduce anxieties and promote trust, meaning that they would be more

likely to find a way to overcome perceived barriers in order to take part in a study.

### Limitations

Despite people from 13 countries across 5 continents completing the study, the results are still limited by a relatively small sample size. It should also be highlighted that participants in the study are potentially biased towards those already interested in research and to those who are actively engaged with FXS communities in the United Kingdom and on-line. Thus, these results must be seen in the context of barriers to research for those who are at least already contemplative of participation in research. Potential barriers were suggested in the questionnaire and, therefore, may have influenced the responses given; in particular, we did not include inclusion in the placebo arm as one of the specific barriers suggested, which may explain why this was not considered to be an issue by focus groups. However, the focus groups were carried out over 6 months after the questionnaire was completed, which likely reduced the risk of participants from focusing on only the suggested potential barriers. Finally, we did not systematically collect information around participant gender and were therefore unable to analyse whether there were differences between male and female patients.

### Implications for future medication trial design

When designing clinical trials for FXS, researchers should bear in mind the factors identified as barriers to participation in this study as well as the potential strategies for overcoming them. Such strategies should include the following:

- 1 Providing more information in accessible and easy-to-understand formats, including as much safety data as, is possible.
- 2 Holding information evenings where families can meet the research team and ask questions.
- 3 Providing materials to help people with FXS familiarise themselves with the research environment and team in advance.
- 4 Providing medication in different preparations
- 5 When blood tests are required, provide information to help prepare individuals with FXS for this. If possible, design a desensitisation programme to facilitate blood testing.

- 6 Consider the number of visits needed for the study and the travel and time that would be required, looking at whether it would be feasible to do a combination of local, remote and more distant site visits if required.

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## Conflict of interests

AS and AGM have previously undertaken clinical trials of medications for fragile X syndrome funded by Novartis and Roche. AGM has previously sat on a Scientific Advisory Board to GW Pharma on clinical trial design.

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**Supporting Information**

Additional Supporting Information may be found online in the supporting information tab for this article.

**Data S1.** Supporting Information